Scientific Abstract

Annually, 42,000 cases of squamous cell carcinoma of the head and neck occur in the United States. This represents about 5% of the total incidence of cancer (1). In 1998, estimates predicted that 12,300 deaths from this disease would occur in the Unites States (2). Early stage disease is treated with surgery, radiotherapy, or a combination of the two. (3,4). Sixty to ninety percent of patients with early stage disease are disease-free at 2 to 5 years of follow-up and are considered cured of their primary malignancy.

Approximately two-thirds of patients present with advanced disease. Treatment of locally advanced, unresectable head and neck cancer represents a particular challenge. The median survival for patients with local or disseminated recurrent squamous cell carcinoma of the head and neck has been reported as 6 months, with 20% of patients surviving at 1 year (5). Chemotherapy (single and multiple agents) and radiation in combination with chemotherapy have demonstrated activity in patients with recurrent or metastatic disease, but have not improved survival rates in these patients.

Cisplatin and its analog carboplatin are considered the most efficacious chemotherapeutic agents in head and neck cancer. Response rates with cisplatin are 20-30%, with occasional observations of complete response (6-8). Taxol-based regimens are also frequently used with relative success in head and neck cancer. (2) Methotrexate is currently regarded as palliative rather than curative therapy. Combination chemotherapy has resulted in significantly higher response rates but has not prolonged survival (10). The combination of cisplatin and 5-fluorouracil demonstrates response rates of 20-70% in patients with recurrent disease (9, 10-15). Chemotherapy regimens offered as neoadjuvant therapy or in combination with radiotherapy have shown promise, but thus far fail to enhance survival In addition, they are associated with significant toxicities (16-22).

Given the generally poor prognosis for advanced disease, there is clearly a need for alternative therapies for the treatment of head and neck cancer. Gene therapy with immunomodulators such as the interferons and interleukins may provide alternative or adjuvant therapy to standard radiation, chemotherapy, and surgery. IL-12 Gene Medicine is being developed for treatment of patients who present with unresectable or recurrent/refractory head and neck cancer .

Human IL-12 mediates a number of biological activities, including enhancement of the proliferation and cytolytic function of T-cells and natural killer (NK) cells (24,25,26). IL-12 induces T-cells and NK cells to produce a number of other cytokines, including IFN-gamma, tumor necrosis factor (TNF), IL-2, IL-3, IL-8, IL-10, and colony-stimulating factors. (29) IFN-gamma is believed to have many biological effects which could influence tumor growth (29). IL-12 also stimulates the generation of T-helper type 1 (Th1) effector cells during an immune response, and can inhibit growth-factor-induced angiogenesis (27,28,29) thereby slowing tumor growth.

Other studies have also suggested a role for endogenous IL-12 in tumor pathophysiology (30,31). Lissoni et.al. (32) evaluated serum levels of endogenous IL-12 in a group of patients with solid tumors, comparing survival times with a group of patients treated with IL-2. Mean serum levels of IL-12 were significantly higher in patients with metastatic disease, than in those with local disease only. Within the metastatic group, patients with elevated blood concentrations of IL-12 demonstrated a significantly higher 1 year survival than those with normal IL-12 values.These data suggest that higher levels of IL-12 may have favorable prognostic significance in solid tumor patients, either in baseline conditions or after treatment with cytokine therapy. Lissoni et. al. (33) investigated the acute endocrine effects of IL-12 in patients with metastatic renal cell cancer. The

results suggested that IL-12 may act as a biological response modifier, not only on the immune system, but also on neuroendocrine functions.

IL-12 has been demonstrated to have potent antitumor activity in animal models. However, studies of the recombinant protein in patients have been limited due to the occurrence of the dose limiting toxicities. By administering gene therapy, more physiologically compatible levels of IL-12 may be generated than those seen with the recombinant protein. On the basis of the pre-clinical work with IL-12 Gene Medicine, tumor shrinkage is expected, and stimulation of host immunity may reduce tumor burden in regional and distant sites.

The primary aim of the study is to evaluate the safety of direct intratumoral injection of a gene encoding IL-12. The clinical study proposed will also evaluate delivery of human IL-12 to a tumor site injected with a non-viral, polymer-mediated gene encoding IL-12. This gene transfer is intended to induce local (intra- or peri-tumoral) expression of IL-12 at levels sufficient to promote an anti-tumor response without potentially toxic systemic concentrations of IL-12 protein. Animal experiments were conducted to address this safety issue. Serum concentrations of IL-12 protein after injection of the Gene Medicine were many times lower than those associated with the administration of the recombinant protein calculated on an equivalent mg/kg basis(34) Preclinical safety and toxicology testing in non-human primates also supports the safety of this approach. Up to 18 mg/kg of the IL-12 Gene Medicine was administered to the Cynomolgus monkey, a dose 20 times greater than the highest dose intended for administration to human subjects (9 mg).

Disease progression in patients enrolled in this trial will be monitored both clinically and radiographically, by CT imaging. Time to progressive disease has been found to correlate with improved survival and may be a useful surrogate marker for the latter (23). In addition, time to progressive disease may be a measure of the patient's ability to enjoy a better quality of life. Time to progressive disease, therefore, has been selected as a secondary endpoint for the current study.

References:

1. Wingo PA, Tong T, Bolden S. Cancer statistics 1995. CA. 1995; 45: 8 – 30.
2. Shin DM, Glisson BS, Khuri FR, Ginsberg L, Papadimitrakapoulou V, Lee JJ, Lawhorn K, Gillenwater AM, Ang K, Clayman GL, Callender DL, Hong WK, Lippman SM. Phase II trial of paclitaxel, ifosfamide, and cisplatin in patients with recurrent head and neck squamous cell carcinoma. Journal of Clinical Oncology 1998; 16 (4): 1325 – 1330.
3. Wenig BL. The role of surgery in head and neck cancer: Standard care and new horizons. Semin Onco. 1994; 21: 289 – 295.
4. Sweeney PJ, Haraf DJ, Vokes EE, Dougherty M, Weichselbaum RR. Radiation therapy in head and neck cancer: indications and limitations. Semin Oncol. 1994; 21: 296 – 303.
5. Wolf G, Lippman SM, Laramore G, Hong WK. Head and neck cancer *in* Cancer Medicine, 3rd edition, Holland JF, Frei E, Bast RC Jr, Kufe DW, Morton DL, Weichselbaum R (eds.). Philadelphia Lea Febiger, 1993; pp. 1211 – 1275.